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ANTIULCER AGENT

(Kokaiyo Zai)

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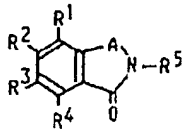
SPECIFICATION

I. Title of the Invention

Antiulcer Agent

II. Claims

An agent for preventing or treating ulcer, which contains a benzisothiazolone derivative expressed by a general formula



(I)

(where R^1, R^2, R^3 and R^4 are same or different and represent a hydrogen atom, lower alkyl, aralkyl, or aralkyl substitued by one or more groups selected from the following [substituent group A], lower alkoxy or halogen atom, respectively,

A represents a sulfur atom, solufoxide or sulfone group,

R^5 represents a hydrogen atom, lower alkyl, lower alkyl substituted by one or more groups selected from the following [substituent group A], alkenyl, alkenyl substituted by one or more groups selected from the following [substituent group A], aryl,

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[1] Numbers in the margin indicate pagination in the foreign text.

aryl substituted by one or more groups selected from the following [substituent group B], heterocyclic group, heterocyclic group or cycloalkyl substituted by one or more groups selected from the following [substituent group C],

or its salt.

[Substituent group A]

aryls, hydroxyls, cyano, lower alkylthios, lower alkoxycarbonyls and aralkyloxycarbonyls.

[Substituent group B]

lower alkyls, lower alkoxyls, halogen atoms, lower halogenoalkyls, aminos which may also be substituted by lower alkyls, cyano, carboxyls, carbamoyls, lower alkoxycarbonyls and aralkyloxycarbonyls.

[Substituent group C]

lower alkyls, lower halogenoalkyls, lower alkoxyls, halogen atoms, oxo, aryls, aryls and aralkyloxyls substituted by one or more group selected from the above [Substituent group B].

III. Detailed Description of the Invention]

[Purpose]

[Field of Industrial Application]

This invention relates to an excellent agent for preventing or treating ulcer containing a benzisothiazolone derivative.

[Prior Art]

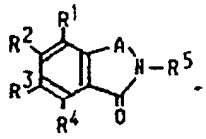
It has been known that 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-5-methoxy-(1H)-benzimidazole(omeprazole) (a compound described in Japan Kokai 54—141783) is clinically effective for suppressing gastric acid secretion as antiulcer agent by inhibiting H^+,K^+-adenosine triphosphatase (abbreviated as H^+,K^+-ATPase hereafter) which is an enzyme relating to the final stage of gastric acid secretion.

[Problem to Be Solved by the Invention]

The inventors made earnest studies on synthesis of benziso-thiazolone derivatives and their phamacological activity for years, consequently they discovered that the compounds of this invention have an enzymic inhibition activity of H^+,K^+-adenosine triphosphatase over 100 times as much as that of above known omeprazole and become an excellent agent for preventing and treating ulcer, thus came to accomplish this invention.

[Constitution]

The invented novel agent for preventing and treating ulcer contains a benzisothiazolone derivative expressed by a general formula



(I)

(where R^1, R^2, R^3 and R^4 are same or different and represent a hydrogen atom, lower alkyl, aralkyl, or aralkyl substitued by one or more groups selected from the following ⌈substituent group A⌋, lower alkoxyl or halogen atom, respectively,

A represents a sulfur atom, solufoxide or sulfone group,

R^5 represents a hydrogen atom, lower alkyl, lower alkyl substituted by one or more groups selected from the following ⌈substituent group A⌋, alkenyl, alkenyl substituted by one or more groups selected from the following ⌈substituent group A⌋, aryl, aryl substituted by one or more groups selected from the following ⌈substituent group B⌋, heterocyclic group, heterocyclic group or cycloalkyl substituted by one or more groups selected from the following ⌈substituent group C⌋,

or its salt.

⌈Substituent group A⌋

aryls, hydroxyls, cyano, lower alkylthios, lower alkoxycarbonyls and aralkyloxycarbonyls.

⌈Substituent group B⌋

lower alkyls, lower alkoxyls, halogen atoms, lower halogenoalkyls, aminos which may also be substituted by lower alkyls, cyano, carboxyls, carbamoyls, lower alkoxycarbonyls and aralkyloxycarbonyls.

⌈Substituent group C⌋

lower alkyls, lower halogenoalkyls, lower alkoxyls, halogen atoms, /3

oxo, aryls, aryls and aralkyloxyls substituted by one or more group selected from the above ⌈Substituent group B⌋.

In the above general formula (I), ⌈lower alkyls⌋ in the definition of R^1, R^2, R^3, R^4 and R^5, ⌈lower alkyls⌋ of ⌈lower alkyls substituted by one or more groups selected from the following ⌈substituent group A⌋⌋ in the definition of R^5, ⌈lower alkyls⌋ in definition of ⌈substituent group B⌋ and ⌈lower alkyls⌋ in the definition of ⌈substituent group C⌋ represent C_1 - C_6

linear or branched alkyls, e. g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl, n-pentyl, isopentyl, 2-methylbutyl, neopentyl, n-hexyl, 4-methylpentyl, 3-methylpentyl, 2-methyl-pentyl, 3,3-dimethylbutyl, 2,2-dimethyl-butyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, etc., and they are suitably C_1 - C_4 linear or branched alkyls.

⌈Aralkyls⌋ in the definition of R^1, R^2, R^3 and R^4 and ⌈aralkyls⌋ of ⌈aralkyls substituted by one or more groups selected from the following ⌈substituent group B⌋⌋ in the definition of R^1, R^2, R^3 and R^4 mean groups in which an ⌈aryl⌋ described later is bonded to said ⌈lower alkyls⌋, e. g., benzyl, ∀-naphthylmethyl, ∃-naphthyl-methyl, diphenylmethyl, triphenylmethyl, ∀-naphthyl-diphenyl-methyl, 9-anthrylmethyl, piperonyl, 1-phenetyl, 2-phenetyl, 1-naphthylethyl, 2-naphthylethyl, 1-phenylpropyl, 2-phenylpropyl, 3-phenylpropyl, 1-phenylbutyl, 2-phenylbutyl, 3-phenylbutyl, 4-phenylbutyl, 1-naphthylbutyl, 2-naphthylbutyl, 3-naphthylbutyl, 4-naphthylbutyl, 1-phenylpentyl, 2-phenylpentyl, 3-phenylpentyl, 4-phenylpentyl, 5-phenylpentyl, 1-naphthyl-pentyl, 2-naphthyl-pentyl, 3-naphthylpentyl, 4-naphthylpentyl, 5-naphthylpentyl, 1-phenylhexyl, 2-phenylhexyl, 3-phenylhexyl, 4-phenylhexyl, 5-phenylhexyl, 6-phenylhexyl, 1-naphthylhexyl, 2-

naphthylhexyl, 3-naphthylhexyl, 4-naphthylhexyl, 5-naphthyl-hexyl, 6-naphthyl-hexyl, etc. can be given, and they are suitably C_1 - C_3 linear or branched aryl-substituted alkyls.

As the 「aralkyls substituted by one or more groups selected from the following 「substituent group B」」, e. g., aralkyl substituted by lower alkyl(s) such as 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methylphenetyl, 4-methylphenetyl, 2-ethylbenzyl, 3-propylphenetyl, 4-ethylbenzyl, 2-butylphenetyl, 3-pentylbenzyl, 4-pentylphenetyl, 3,5-dimethylbenzyl, 2,5-dimethylphenetyl, 2,6-dimethylbenzyl, 2,4-dimethylphenetyl, 3,5-dibutylbenzyl, 2,5-dipentylphenetyl, 2,6-dipropylbenzyl, 2,4-

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dipropylphenetyl, 2,3,6-trimethylbenzyl, 2,3,4-trimethylphenetyl, 3,4,5-trimethylbenzyl, 2,4,6-trimethylbenzyl, 2,5,6-trimethylphenetyl, 2,3,6-tributylphenetyl, 2,3,4-tripentylbenzyl, 3,4,5 tributylphenetyl, 2,5,6-tripropylbenzyl, 2,4,6-tripropylphenetyl, 1-methyl-2-naphthylmethyl, 2-methyl-1-naphthylethyl, 3-methyl-1-naphthylmethyl, 1-ethyl-2-naphthylethyl, 2-propyl-1-naphthylmethyl, 3-butyl-1-naphthylethyl, 3,8-dimethyl-1-naphthylmethyl, 2,3-dimethyl-1-naphthylethyl, 4,8-dimethyl-1-naphthylmethyl, 5,6-dimethyl-1-naphthylethyl, 3,8-diethyl-1-naphthylmethyl, 2,3-dipropyl-1-naphthylmethyl, 4,8-dipentyl-1-naphthylethyl, 5,6-dibutyl-1-naphthylmethyl, 2,3,6-trimethyl-1-naphthyl-

methyl, 2,3,4-trimethyl-1-naphthylethyl, 3,4,5-trimethyl-1-naphthylmethyl, 4,5,6-trimethyl-1-naphthylmethyl, 2,4,8-trimethyl-1-naphthylmethyl, bis(2-methylphenyl)methyl, 3-methylphenylphenylmethyl, bis(4-methylphenyl)methyl, 4-methylphenylphenylmethyl, bis(2-ethylphenyl)methyl, bis(3-ethylphenyl)methyl, bis(4-ethylphenyl)methyl, 2-propylphenylphenylmethyl, 3-propylphenylphenylmethyl, bis(4-propylphenyl)methyl, bis(3,5-dimethylphenyl)-methyl, bis(2,5-dimethylphenyl)methyl, bis(2,6-dimethylphenyl)-methyl, 2,4-dimethylphenylphenylmethyl, 2,5-dipropylphenylphenylmethyl, 2,6-dipropylphenylphenylmethyl, bis(2,4-diethylphenyl)methyl, bis(2,3,6-trimethylphenyl)methyl, etc.; aralkyls substituted by lower alkoxyl(s) such as 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 3-methoxyphenetyl, 2-ethoxyphenetyl, 3-propoxybenzyl, 4-ethoxyphenetyl, 2-butoxybenzyl, 3-pentoxyphenetyl, 4-pentoxybenzyl, 3,5-dimethoxyphenetyl, 2,5-dipentoxybenzyl, 2,6-dimethoxyphenetyl, 2,4-dimethoxybenzyl, 3,5-dibutoxybenzyl, 2,5-dipentoxybenzyl, 2,6-dipropoxyphenetyl, 2,4-dipropoxybenzyl, 2,3,6-trimethoxyphenetyl, 2,3,4-trimethoxybenzyl, 3,4,5-trimethoxyphenetyl, 2,5,6-trimethoxybenzyl, 2,4,6-trimethoxyphenetyl, 2,3,6-tributoxybenzyl, 2,3,4-tripentoxyphenetyl, 3,4,5-tributoxybenzyl, 2,5,6-tripropoxyphenetyl, 2,4,6-tripropoxybenzyl, 1-methoxy-2-naphthylmethyl, 2-methoxy-1-naphthylmethyl, 3-methoxy-1-naphthylethyl, 1-ethoxy-2-naphthyl-

methyl, 2-propoxy-1-naphthylmethyl, 3-butoxy-1-naphthylethyl, 3,8-dimethoxy-1-naphthylmethyl, 2,3-dimethoxy-1-naphthylmethyl, 4,8-dimethoxy-1-naphthylethyl, 5,6-dimethoxy-1-naphthylmethyl, 3,8-diethoxy-1-naphthylmethyl, 2,3-dipropoxy-1-naphthylethyl, 4,8-dipentoxy-1-naphthylmethyl, 5,6-dibutoxy-1-naphthylmethyl, 2,3,6-trimethoxy-1-naphthylethyl, 2,3,4-trimethoxy-1-naphthylmethyl, 3,4,5-trimethoxy-1-naphthylmethyl, 4,5,6-trimethoxy-1-naphthylethyl, 2,4,8-trimethoxy-1-naphthylmethyl, bis(2-methoxyphenyl)methyl, 3-methoxyphenylphenylmethyl, bis(4-methoxyphenyl)methyl, 4-methoxyphenylphenylmethyl, bis(2-ethoxyphenyl)methyl, bis(3-ethoxyphenyl)methyl, bis(4-ethoxy-phenyl)methyl, 2-propoxyphenylphenylmethyl, 3-propoxyphenylphenylmethyl, bis(4-propoxyphenyl)methyl, bis(3,5-dimethoxyphenyl)methyl, bis(2,5-dimethoxyphenyl)methyl, bis(2,6-dimethoxyphenyl)methyl, 2,4-dimethoxyphenylphenylmethyl, bis(3,5-dipropoxyphenyl)methyl, 2,5-dipropoxyphenylphenylmethyl, 2,6-/5 diethoxyphenylphenylmethyl, bis(2,4-diethoxyphenyl)methyl, bis(2,3,6-trimethoxyphenyl)methyl, etc.; aralkyls substituted by halogen atom(s) such as 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3,5-difluorobenzyl, 2,5-difluorophenetyl, 2,6-difluorobenzyl, 2,4-difluorophenetyl, 3,5-dibromobenzyl, 2,5-dibromophenetyl, 2,6-dichlorobenzyl, 2,4-

dichlorophenetyl, 2,3,6-trifluorobenzyl, 2,3,4-trifluorophenetyl, 3,4,5-trifluorobenzyl, 2,5,6-trifluorophenetyl, 2,4,6-trifluorobenzyl, 2,3,6-tribromophenetyl, 2,3,4-tribromobenzyl, 3,4,5-tribromophenetyl, 2,5,6-trichlorobenzyl, 2,4,6-trichlorophenetyl, 1-fluoro-2-naphthylmethyl, 2-fluoro-1-naphthylethyl, 3-fluoro-1-naphthylmethyl, 1-chloro-2-naphthylethyl, 2-chloro-1-naphthylmethyl, 3-bromo-1-naphthylethyl, 3,8-difluoro-1-naphthylmethyl, 2,3-difluoro-1-naphthylethyl, 4,8-difluoro-1-naphthylmethyl, 5,6-difluoro-1-naphthylethyl, 3,8-dichloro-1-naphthylmethyl, 2,3-dichloro-1-naphthylethyl, 4,8-dibromo-1-naphthylmethyl, 5,6-dibromo-1-naphthylethyl, 2,3,6-trifluoro-1-naphthylethyl, 2,3,4-trifluoro-1-naphthylethyl, 3,4,5-trifluoro-1-naphthylmethyl, 4,5,6-trifluoro-1-naphthylethyl, 2,4,8-trifluoro-1-naphthylmethyl, bis(2-fluorophenyl)methyl, 3-fluorophenylphenylmethyl, bis(4-fluorophenyl)methyl, 4- fluorophenylphenylmethyl, bis(2-chlorophenyl)methyl, bis(3-chlorophenyl)-methyl, bis(4-chlorophenyl)methyl, 4-chlorophenylphenylmethyl, 2-bromophenylphenylmethyl, 3-bromophenylphenylmethyl, bis(4-bromophenyl)methyl, bis(3,5-difluorophenyl)methyl, bis(2,5-difluorophenyl)methyl, bis(2,6-didifluorophenyl)methyl, 2,4-difluorophenylphenylmethyl, bis(3,5-dibromophenyl)methyl, 2,5-dibromophenylphenylmethyl, 2,6-dichlorophenylphenylmethyl, bis(2,4-dichlorophenyl)methyl, bis(2,3,6-trifluorophenyl)methyl,

etc.; aralkyls substituted by lower halogenoalkyl(s) such as 2-trifluoromethylbenzyl, 3-trifluoromethylphenetyl, 4-trifluoro-methylbenzyl, 2-trichloromethylphenetyl, 3-trichloromethyl-benzyl, 4-trifluoro-methylphenetyl, 2-tribromomethylbenzyl, 3-tribromomethylphenetyl, 4-tribromomethylbenzyl, 3,5-bistri-fluoromethylphenetyl, 2,5-bistrifluorobenzyl, 2,6-difluoro-methylphenetyl, 2,4-bistrifluoromethylbenzyl 3,5-bistrifluoro-methylphenetyl, 2,5-bisdibromomethylbenzyl, 2,6-bisdichloro-methylmethylphenetyl, 2,4-bisdichloromethylbenzyl, 2,3,6-tris-trifluoromethylphenetyl, 2,3,4-tristrifluoromethylbenzyl, 3,4,5-tristrifluoromethylphenetyl, 2,5,6-tristrifluoromethylbenzyl, 2,4,6-tristrifluoromethylphenetyl, 2,3,6-tristribromomethyl-benzyl, 2,3,4-trisdibromomethylphenetyl, 3,4,5-tristribromo-methylbenzyl, 2,5,6-trisdichloromethylmethylphenetyl, 2,4,6-trisdichloromethylbenzyl, 1-trifluoromethyl-2-naphthylethyl, 2-trifluoromethyl-2-naphthylmethyl, 3-trifluoromethyl-1-naphthyl-ethyl, 1-trichloromethyl-2-naphthylmethyl, 2-dichloromethyl-1-naphthylethyl, 3-tribromomethyl-1-naphthylmethyl, 3,8-bistrifluoromethyl-1-naphthylethyl, 2,3-bistrifluoromethyl-1-naphthylmethyl, 4,8-bistrifluoromethyl-1-naphthylethyl, 5,6-bistrifluoromethyl-1-naphthylmethyl, 3,8-bistrichloromethyl-1-naphthylethyl, 2,3-bisdichloromethyl-1-naphthylethyl, 4,8-bisdi-bromomethyl-1-naphthylethyl, 5,6-bistribromomethyl-1-naphthyl-

methyl, 2,3,6-tristrifluoromethyl-1-naphthylethyl, 2,3,4-tristrifluoromethyl-1-naphthylmethyl, 3,4,5-tristrifluoromethyl-1-naphthylethyl, 4,5,6-tristrifluoromethyl-1-naphthylmethyl, 2,4,8-tristrifluoromethyl-1-naphthylmethyl, bis(4-trifluoromethylphenyl)methyl, 4-trifluoromethylphenylphenylmethyl, bis(2-trichloromethylphenyl)methyl, bis(3-trichloromethylphenyl)-methyl, bis(4-trichloromethylphenyl)methyl, 2-tribromomethylphenylphenylmethyl, 3-tribromomethylphenylphenylmethyl, bis(4-tribromomethylphenyl)methyl, bis(3,5-bistrifluoromethylphenyl)-methyl, bis(2,5-bistrifluoromethylphenyl)methyl, bis(2,6-bistrifluoromethylphenyl)methyl, 2,4-bistrifluoromethylphenyl)-methyl, bis(3,5-bistribromomethylphenyl)methyl, 2,5-bistribromomethylphenylphenylmethyl, 2,6-bistrichloromethylphenylphenylmethyl, bis(2,4-bistrichloromethylphenyl)methyl, bis(2,3,6-tristrifluoromethylphenyl)methyl, etc.; aralkyls substituted by aminos which may also be substituted by lower alkyl(s) such as 2-aminophenetyl, 3-aminobenzyl, 4-aminophenetyl, 3,5-diaminobenzyl, 2,5-diaminophenetyl, 2,6-diaminobenzyl, 2,4-diaminophenetyl, 2,4-diaminophenetyl, 2,3,6-triaminobenzyl, 2,3,4-triaminophenetyl, 3,4,5-triaminobenzyl, 2,5,6-triaminophenetyl, 2,4,6-triaminobenzyl, 1-amino-2-naphthylmethyl, 2-amino-1-naphthylethyl, 3-amino-1-naphthylmethyl, 3,8-diamino-1-naphthylmethyl, 2,3-diamino-1-naphthylethyl, 4,8-diamino-1-naphthyl-

methyl, 5,6-diamino-1-naphthylmethyl, 2,3,6-triamino-1-naphthylethyl, 2,3,4-triamino-1-naphthylmethyl, 3,4,5-triamino-1-naphthylmethyl, 4,5,6-triamino-1-naphthylethyl, 2,4,8-triamino-1-naphthylmethyl, bis(2-aminophenyl)methyl, 3-aminophenylphenylmethyl, bis(4-aminophenyl)methyl, 4-aminophenylphenylmethyl, bis(3,5-diaminophenyl)methyl, bis(2,5-diaminophenyl)methyl, bis(2,6-diaminophenyl)methyl, 2,4-diaminophenylphenylmethyl, bis(2,3,6-triaminophenyl)methyl, etc.; aralkyls substituted by cyano(s) such as 2-cyanophenetyl, 3-cyanobenzyl, 4-cyanobenzyl, 4-cyanobenzyldiphenylmethyl, 4-cyanophenetyl, 3,5-dicyanobenzyl, 2,5-dicyanophenetyl, 2,6-dicyanobenzyl, 2,4-dicyanophenetyl, 2,3,6-tricyanobenzyl, 2,3,4-tricyanophenetyl, 3,4,5-tricyanobenzyl, 2,5,6-tricyanoophenetyl, 2,4,6-tricyanobenzyl, 1-cyano-2-naphthylmethyl, 3-cyano-1-naphthylmethyl, 3,8-dicyano-1-naphthylmethyl, 2,3-dicyano-1-naphthylethyl, 4,8-dicyano-1-naphthylmethyl, 5,6-dicyano-1-naphthylmethyl, 2,3,6-tricyano-1-naphthylethyl, 2,3,4-tricyano-1-naphthylmethyl, 3,4,5-tricyano-1-naphthylmethyl, 4,5,6-tricyano-1-naphthylethyl, 2,4,8-tricyano-1-naphthylethyl, bis(2-cyanophenyl)methyl, 3-cyanophenylphenylmethyl, bis(4-cyanophenyl)methyl, 4-cyanophenylphenylmethyl, bis(3,5-dicyanophenyl)methyl, bis(2,5-dicyanophenyl)methyl, bis(2,6-dicyanophenyl)methyl, 2,4-dicyanophenylphenylmethyl, bis(2,3,6-tricyanophenyl)methyl, etc.; aralkyls

substituted by carboxyl(s) such as 2-carboxyphenetyl, 3-carboxybenzyl, 4-carboxyphenetyl, 3,5-dicarboxybenzyl, 2,5-dicarboxy-

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phenetyl, 2,6-dicarboxybenzyl, 2,4-dicarboxyphenetyl, bis(2-carboxyphenyl)methyl, 3-carboxyphenylphenylmethyl, bis(4-carboxyphenyl)methyl, 4-carboxyphenylphenylmethyl, bis(3,5-dicarboxyphenyl)methyl, bis(2,5-dicarboxyphenyl)methyl, bis(2,6-dicarboxyphenyl)methyl, 2,4-dicarboxyphenylphenylmethyl, bis-(2,3,6-tricarboxyphenyl)methyl, etc.; aralkyls substituted by carbamoyl(s) such as 2-carbamoylbenzyl, 3-carbamoylphenetyl, 4-carbamoylbenzyl, 3,5-dicarbamoylphenetyl, 2,5-dicarbamoylbenzyl, 2,6-dicarbamoylphenetyl, 2,4-dicarbamoylbenzyl, bis(2-carbamoylphenyl)methyl, 3-carbamoylphenylphenylmethyl, bis(4-carbamoylphenyl)methyl, 4-carbamoylphenylphenylmethyl, bis(3,5-dicarbamoylphenyl)methyl, bis(2,5-dicarbamoylphenyl)methyl, bis(2,6-dicarbamoylphenyl)methyl, 2,4-dicarbamoylphenylphenyl-methyl, bis(2,3,6-tricarbamoylphenyl)methyl, etc.; aralkyls substituted by alkoxycarbonyl(s) such as 2-methoxycarbonylbenzyl, 3-methoxycarbonylbenzyl, 4-methoxycarbonylbenzyl, 2-ethoxy-carbonylbenzyl, 3-ethoxycarbonylbenzyl, 4-ethoxycarbonylbenzyl, 2-methoxycarbonylphenetyl, 3-methoxycarbonylphenetyl, 4-methoxy-carbonylphenetyl, 2-ethoxycarbonylphenetyl, 3-ethoxycarbonyl-phenetyl, 4-ethoxycarbonylphenetyl, etc.; aralkyls substituted

by aralkyloxycarbonyl(s) such as 2-benzyloxycarbonylbenzyl, 3-benzyloxycarbonylbenzyl, 4-benzyloxycarbonylbenzyl, 2-benzyloxycarbonylphenetyl, 3-benzyloxycarbonylphenetyl, 4-benzyloxycarbonylphenetyl, etc. can be given.

⌈Lower alkoxyls⌋ in the definition of R^1, R^2, R^3 and R^4, ⌈lower alkoxyls⌋ in the definition of ⌈substituent group B⌋, ⌈lower alkyls⌋ in the definition of ⌈substituent group C⌋ mean groups given by bonding an oxygen atom to the said ⌈lower alkoxyls⌋, e. g., they represent C_1 - C_4 linear or branched alkoxyls such as methoxyl, ethoxyl, n-propoxyl, isopropoxyl, n-butoxyl, isobutoxyl, s-butoxyl, t-butoxyl, n-pentoxyl, isopentoxyl, 2-methylbutoxyl, neopentoxyl, n-hexyloxyl, 4-methylpentoxyl, 3-methylpentoxyl, 2-methylpentoxyl, 3,3-dimethylbutoxyl, 2,2-dimethylbutoxyl, 1,1-dimethylbutoxyl, 1,2-dimethylbutoxyl, 1,3-dimethylbutoxyl, 2,3-dimethylbutoxyl, etc., and they are suitably C_1 - C_4 linear or branched alkoxyls.

⌈Halogen atoms⌋ in the definition of R^1, R^2, R^3 and R^4, ⌈halogen atoms⌋ in the definition of ⌈substituent group B⌋ and ⌈lower alkyls⌋ in the definition of ⌈substituent groups C⌋ represent fluorine, chlorine or iodine.

As ⌈alkenyls⌋ in the definition of R^5 and ⌈alkenyls⌋ of ⌈alkenyls substituted by one or more groups selected from the following ⌈substituent groups A⌋, C_3 - C_6 linear or branched alkenyls such as 2-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-ethyl-2-propenyl, 2-butenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 1-ethyl-2-butenyl, 3-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 1-ethyl-3-butenyl, 2-pentenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-pentenyl, 1-methyl-3-pentenyl, 2-methyl-3-pentenyl, 4-pentenyl, 1-methyl-4-pentenyl, 2-methyl-4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl,

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etc. can be given, and they are suitably C_3 - C_4 linear or branched alkenyls.

As ⌈aryls⌋ in the definition of R^5 and ⌈aryls⌋ of ⌈aryls substituted by one or more groups selected from ⌈substituent group B⌋⌋, ⌈aryls⌋ in the definition of ⌈substituent groups A⌋ and ⌈aryls⌋ in the definition of ⌈substituent groups C⌋ and ⌈aryls⌋ of ⌈aryls substituted by one or more groups selected from above ⌈substituent group B⌋⌋, e. g., C_6 - C_{14} aromatic hydrocarbyls such as phenyl, naphthyl, etc. can be given, and they are suitably phenyl.

As 「aryls substituted by one or more groups selected from above 「substituent group B」」, e. g., aryls substituted by lower alkyl(s) such as 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 2-butylphenyl, 3-pentylphenyl, 4-pentylphenyl, 3,5-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 2,4-dimethylphenyl, 3,5-dibutylphenyl, 2,5-dipentylphenyl, 2,6-dipropylmethylphenyl, 2,4-dipropylphenyl, 2,3,6-trimethylphenyl, 2,3,4-trimethylphenyl, 3,4,5-trimethylphenyl, 2,5,6-trimethylphenyl, 2,4,6-trimethylphenyl, 2,3,6-tributylphenyl, 2,3,4-tripentylphenyl, 3,4,5-tributylphenyl, 2,5,6-tripropylmethylphenyl, 2,4,6-tripropylphenyl, 1-methyl-2-naphthyl, 2-methyl-1-naphthyl, 3-methyl-1-naphthyl, 1-ethyl-2-naphthyl, 2-propyl-1-naphthyl, 3-butyl-1-naphthyl, 3,8-dimethyl-1-naphthyl, 2,3-dimethyl-1-naphthyl, 4,8-dimethyl-1-naphthyl, 5,6-dimethyl-1-naphthyl, 3,8-diethyl-1-naphthyl, 2,3-dipropyl-1-naphthyl, 5,6-dibutyl-1-naphthyl, 2,3,6-trimethyl-1-naphthyl, 2,3,4-trimethyl-1-naphthyl, 3,4,5-trimethyl-1-naphthyl, 4,5,6-trimethyl-1-naphthyl, 2,4,8-trimethyl-1-naphthyl, etc.; aryls substituted by lower alkoxyl(s) such as 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-propoxyphenyl, 4-ethoxyphenyl, 2-butoxyphenyl, 3-pentoxyphenyl, 4-pentoxyphenyl, 3,5-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 2,4-dimethoxyphenyl, 3,5-

dibutoxyphenyl, 2,5-dipentoxyphenyl, 2,6-dipropoxyphenyl, 2,6-diisopropoxyphenyl, 2,4-dipropoxyphenyl, 2,3,6-trimethoxyphenyl, 2,3,4-trimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2,5,6-trimethoxyphenyl, 2,4,6-trimethoxyphenyl, 2,3,6-tributoxyphenyl, 2,3,4-tripentoxyphenyl, 3,4,5-tributoxyphenyl, 2,5,6-tripropoxyphenyl, 2,4,6-tripropoxyphenyl, 1-methoxy-2-naphthyl, 2-methoxy-1-naphthyl, 3-methoxy-1-naphthyl, 1-ethoxy-2-naphthyl, 2-propoxy-1-naphthyl, 3-butoxy-1-naphthyl, 3,8-dimethoxy-1-naphthyl, 2,3-dimethoxy-1-naphthyl, 4,8-dimethoxy-1-naphthyl, 5,6-dimethoxy-1-naphthyl, 3,8-diethoxy-1-naphthyl, 2,3-dipropoxy-1-naphthyl, 4,8-dipentoxy-1-naphthyl, 5,6-dibutoxy-1-naphthyl, 2,3,6-trimethoxy-1-naphthyl, 2,3,4-trimethoxy-1-naph-thyl, 3,4,5-trimethoxy-1-naphthyl, 4,5,6-trimethoxy-1-naphthyl, 2,4,8-trimethoxy-1-naphthyl, etc.; aralkyls substituted by halogen atom(s) such as 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,4-difluorophenyl, 3,5-dibromo-/9 phenyl, 2,5-dibromophenyl, 2,6-dichlorophenyl, 2,4-dichlorophenyl, 2,3,6-trifluorophenyl, 2,3,4-trifluorophenyl, 3,4,5-trifluorophenyl, 2,5,6-trifluorophenyl, 2,4,6-trifluorophenyl, 2,3,6-tribromophenyl, 2,3,4-tribromophenyl, 3,4,5-tribromophenyl, 2,5,6-trichlorophenyl, 2,4,6-trichlorophenyl, 1-fluoro-

2-naphthyl, 2-fluoro-1-naphthyl, 3-fluoro-1-naphthyl, 1-chloro-2-naphthyl, 2-chloro-1-naphthyl, 3-bromo-1-naphthyl, 3,8-difluoro-1-naphthyl, 2,3-difluoro-1-naphthyl, 4,8-difluoro-1-naphthyl, 5,6-difluoro-1-naphthyl, 3,8-dichloro-1-naphthyl, 2,3-dichloro-1-naphthyl, 4,8-dibromo-1-naphthyl, 5,6-dibromo-1-naphthyl, 2,3,6-trifluoro-1-naphthyl, 2,3,4-trifluoro-1-naphthyl, 3,4,5-trifluoro-1-naphthyl, 4,5,6-trifluoro-1-naphthyl, 2,4,8-trifluoro-1-naphthyl, etc.; aryls substituted by lower halogenoalkyl(s) such as 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-trichloromethylphenyl, 3-trichloromethylphenyl, 4-trichloromethylphenyl, 2-tribromomethylphenyl, 3-dibromomethylphenyl, 4-dibromomethylphenyl, 3,5-bistrifluoromethylphenyl, 2,5-bistrifluoromethylphenyl, 2,6-bistrifluoromethylphenyl, 2,4-bistrifluoromethylphenyl, 3,5-bistribromophenetyl, 2,5-bisdibromomethylphenyl, 2,6-bisdichloromethylmethylphenyl, 2,4-bisdichloromethymethylphenyl, 2,3,6-tristrifluoromethylphenyl, 2,3,4-tristrifluoromethylphenyl, 3,4,5-tristrifluoromethylphenyl, 2,5,6-tristrifluoromethylphenyl, 2,4,6-tristrifluoromethylphenyl, 2,3,6-tristribromomethylphenyl, 2,3,4-trisdibromomethylphenyl, 3,4,5-tristribromomethylphenyl, 2,5,6-trisdichloromethylmethylphenyl, 2,4,6-trisdichloromethylphenyl, 1-trifluoromethyl-2-naphthyl, 2-trifluoromethyl-1-naphthyl, 3-trifluoromethyl-1-naphthyl, 1-

trichloromethyl-2-naphthyl, 2-dichloromethyl-1-naphthyl, 3-tribromomethyl-1-naphthyl, 3,8-bistrifluoromethyl-1-naphthyl, 2,3-bistrifluoromethyl-1-naphthyl, 4,8-bistrifluoromethyl-1-naphthyl, 5,6-bisdifluoromethyl-1-naphthyl, 3,8-bistrichloromethyl-1-naphthyl, 2,3-bisdichloromethyl-1-naphthyl, 4,8-bisdibromomethyl-1-naphthyl, 5,6-bistribromomethyl-1-naphthyl, 2,3,6-tristrifluoromethyl-1-naphthyl, 2,3,4-tristrifluoromethyl-1-naphthyl, 3,4,5-tristrifluoromethyl-1-naphthyl, 4,5,6-tristrifluoromethyl-1-naphthyl, 2,4,8-tristrifluoromethyl-1-naphthyl, etc.; aryls substituted by amino(s) which may also be substituted by lower alkyl(s) such as 2-aminophenyl, 3-aminophenyl, 4-aminophenyl, 2-methylaminophenyl, 3-methylaminophenyl, 4-methylaminophenyl, 2-dimethylaminophenyl, 3-dimethylaminophenyl, 4-dimethylaminophenyl, 3,5-diaminophenyl, 2,5-diaminophenyl, 2,6-diaminophenyl, 2,4-diaminophenyl, 2,4-diaminophenyl, 2,3,6-triaminophenyl, 2,3,4-triaminophenyl, 3,4,5-triaminophenyl, 2,5,6-triaminophenyl, 2,4,6-triaminophenyl, 1-amino-2-naphthyl, 2-amino-1-naphthyl, 3-amino-1-naphthyl, 3,8-diamino-1-naphthyl, 2,3-diamino-1-naphthyl, 4,8-diamino-1-naphthyl, 5,6-diamino-1-naphthyl, 2,3,6-triamino-1-naphthyl, 2,3,4-triamino-1-naphthyl, 3,4,5-triamino-1-naphthyl, 4,5,6-triamino-1-naphthyl, 2,4,8-triamino-1-naphthyl, etc.;

aralkyls substituted by cyano(s) such as 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 3,5-dicyanophenyl, 2,5-dicyano- /10 phenyl, 2,6-dicyanophenyl, 2,4-dicyanophenyl, 2,3,6-tricyanophenyl, 2,3,4-tricyanophenyl, 3,4,5-tricyanophenyl, 2,5,6-tricyanoophenyl, 2,4,6-tricyanophenyl, 1-cyano-2-naphthyl, 2-cyano-1-naphthyl, 3-cyano-1-naphthyl, 3,8-dicyano-1-naphthyl, 2,3-dicyano-1-naphthyl, 4,8-dicyano-1-naphthyl, 5,6-dicyano-1-naphthyl, 2,3,6-tricyano-1-naphthyl, 2,3,4-tricyano-1-naphthyl, 3,4,5-tricyano-1-naphthyl, 4,5,6-tricyano-1-naphthyl, 2,4,8-tricyano-1-naphthyl, etc.; aryls substituted by carboxyl(s) such as 2-carboxyphenyl, 3-carboxyphenyl, 4-carboxyphenyl, 3,5-dicarboxyphenyl, 2,5-dicarboxyphenyl, 2,6-dicarboxyphenyl, 2,4-dicarboxyphenyl, etc.; aryls substituted by carbamoyl(s) such as 2-carbamoylphenyl, 3-carbamoylphenyl, 4-carbamoylphenyl, 3,5-dicarbamoylphenyl, 2,5-dicarbamoylphenyl, 2,6-dicarbamoylphenyl, 2,4-dicarbamoylphenyl, etc.; aryls substituted by alkoxycarbonyl(s) such as 2-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methoxycarbonylphenyl, 2-ethoxycarbonylphenyl, 3-ethoxycarbonylphenyl, 4-ethoxycarbonylphenyl, 2-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methoxycarbonylphenyl, 2-ethoxycarbonylphenyl, 3-ethoxycarbonylphenyl, 4-ethoxycarbonylphenyl, etc.; and aralkyls substituted by aralkyloxycarbonyl(s) such as 2-benzyloxycarbonylphenyl, 3-benzyloxycarbonylphenyl, 4-

benzyloxycarbonylphenyl, 2-benzyloxycarbonylnaphthyl, 3-benzyloxycarbonylnaphthyl, 4-benzyloxycarbonylnaphtyl, etc. can be given.

As ⌈heterocyclic groups⌋ in the definition of R^5 and ⌈heterocyclic groups⌋ of ⌈heterocyclic groups substituted by one or more groups selected from the following ⌈substituent group B⌋⌋, represent 5- to 14-membered heterocyclic groups which contain a sulfur atom, an oxygen atom and/or 1 to 3 nitrogen atoms and may also be a condensed ring, e. g., furyl, thienyl, pyrrolyl, azepinyl, morpholinyl, thiomorpholinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiozolyl, isothiozolyl, 1,2,3-oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyranyl, pyridyl, quinolyl, isoquinolyl, benzoxazolyl, benzothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, etc. and partial or complete reduction-type groups corresponding to these groups can be given, they suitably 5- to 14-membered heterocyclic groups which contain at least one nitrogen atom, may contain an oxygen atom or sulfur atom and may become a condensed ring, e. g., pyrrolyl, azepinyl, morpholinyl, thiomorpholinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiozolyl, isothiozolyl, 1,2,3-oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyranyl, pyridyl, benzoxazolyl, benzothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, etc. and partial or complete reduction-type groups

corresponding to these groups can be given., they are suitably pyridyl, thiozolyl, isothiozolyl, thiazolidinyl, [4,5]-cyclopentenothiazolyl, [4,5]-cyclohexenothiazolyl, cyclohexenooxazolyl, etc.

⌈Cycloalkyls⌋ in the definition of R^5 represent 3- to 14-membered saturated cyclic hydrocarbyls which may become a condensed ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 8-adamantyl, etc., and they are suitably 5- to 14-membered saturated cyclic hydrocarbyls.

⌈Lower alkylthios⌋ in the definition of ⌈substituent group A⌋ mean groups given by bonding a sulfur atom to said ⌈lower alkyls⌋,

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e. g., represent C_1 - C_6 linear or branched alkylthios such as methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, s-butylthio, t-butylthio, n-pentylthio, isopentylthio, 4-methylbutylthio, neopentylthio, n-hexylthio, 4-methylpentylthio, 3-methylpentylthio, 2-methylpentylthio, 3,3-dimethylbutylthio, 2,2-dimethylbutylthio, 1,1-dimethylbutylthio, 1,2-dimethylbutylthio, 1,3-dimethylbutylthio, 2,3-dimethylbutylthio, etc., and they are suitably C_1 - C_4 linear or branched alkylthios.

⌈Lower alkoxycarbonyls⌋ in the definition of ⌈substituent group A⌋ and ⌈substituent group B⌋ mean groups given by bonding a carbonyl to said ⌈lower alkoxyls⌋.

⌈Lower aralkyloxycarbonyls⌋ in the definition of ⌈substituent group A⌋ and ⌈substituent group B⌋ mean groups given by bonding a carbonyl to ⌈aralkyloxys⌋ described later.

⌈Aminos which may be substituted by ⌈lower aralkyls⌋⌋ in the definition of ⌈substituent group B⌋, e. g., represent aminos substituted by one or two C_1 - C_6 linear or branched alkyls such as amino, methylamino, dimethylamino, ethylamino, diethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, s-butylamino, t-butylamino, n-pentylamino, isopentylamino, 4-methylbutylamino, neopentylamino, n-hexylamino, 4-methylpentylamino, 3-methylpentylamino, 2-methylpentylamino, 3,3-dimethylbutylamino, 2,2-dimethylbutylamino, 1,1-dimethylbutylamino, 1,2-dimethylbutylamino, 1,3-dimethylbutylamino, 2,3-dimethylbutylamino, etc., and they are suitably aminos substituted by one or two C_1 - C_4 linear or branched alkyls.

⌈Lower halogenoalkyls⌋ in the definition of ⌈substituent group C⌋, e. g., represent the said ⌈lower alkyls⌋ substituted by halogen atom(s) such as trifluoromethyl, trichloromethyl, difluoromethyl, dichloromethyl, dibromomethyl, fluoromethyl,

chloromethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 2-bromoethyl, 2-chloroethyl, 2-fluoroethyl, 2,2-dibromoethyl, etc.

⌈Aralkyloxys⌋ in the definition of ⌈substituent group C⌋ mean groups given by bonding an oxygen atom to said ⌈aralkyls⌋.

The compounds (I) of this invention can be made into their salts, and metal salts, e. g., alkali metal salts such as sodium salts, potassium salts, etc.; alkali-earth metal salts such as calcium salts, magnesium salts, etc.; inorganic salts, e. g., hydrohalic acids such as hydrofluorides, hydrochlorides, hydrobromides, hydroiodides, etc.; nitrates, perchlorates, sulfates, phosphates, etc.; lower alkylsulfonates such as methanesulfonates, trifluoromethanesulfonates, ethanesulfonates, etc.; aryl sulfonates such as benzenesulfonates, p-toluene-sulfonates, etc.; organic acid salts such as fumarates, succinates, citrates, tartarates, oxalates, maleates, etc. and amino acid salts such as glutaminates, asparaginates, etc. can be suitably given as such salts.

The compounds (I) of this invention have an asymmetric carbon atom in a molecule and steric isomers being R coordination and S coordination exist, respectively, but all respective compounds or their mixtures are included in this invention.

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As suitable compounds in the compounds (I) contained in the antiulcer agent of this invention,

(1) compounds in which R^1, R^2, R^3, R^4 are same or different and are a hydrogen atom, lower alkyl, lower alkoxyl or halogen atom, respectively,

(2) compounds in which R^1 is a lower alkyl, lower alkoxy or halogen atom

(3) compounds in which R^2 and R^3 are same or different and are a hydrogen atom, lower alkyl, lower alkoxyl or halogen atom, respectively

(4) compounds in which R^4 is a lower alkyl or halogen atom

(5) compounds in which A is a sulfur atom or sulfoxide group

(6) compounds in which A is a sulfur atom

(7) compounds in which R^5 is a lower alkyl substituted by one or more groups selected from the following ⌈substituent group A⌋, an aryl substituted by one or more groups selected from the following ⌈substituent group B⌋ and a heterocyclic group selected from the following ⌈substituent group C⌋

⌈Substituent group A⌋

Aryls, hydroxyl, cyano, lower alkylthios, lower alkoxycarbonyls and aralkyloxycarbonyls.

⌈Substituent group B⌋

Lower alkyls, lower alkoxyls, halogen atoms, lower halogenoalkyls, aminos which may also be substituted by lower alkyls, cyano, carboxyl, carbamoyl, lower alkoxycarbonyls and aralkyloxycarbonyls.

⌈Substituent group C⌋

Lower alkyls, lower halogenoalkyls, lower alkoxyls, halogen atoms, oxo, aryls, aryls and aralkyloxyls substituted by one or more groups selected from the following ⌈substituent group B⌋.

(8) compounds in which R^5 is a lower alkyl substituted by one or more groups selected from the following ⌈substituent group A⌋, an aryl substituted by one or more groups selected from the following ⌈substituent group B⌋ and a heterocyclic group selected from the following ⌈substituent group C⌋

⌈Substituent group A⌋

Aryls, lower alkoxycarbonyls and aralkyloxycarbonyls.

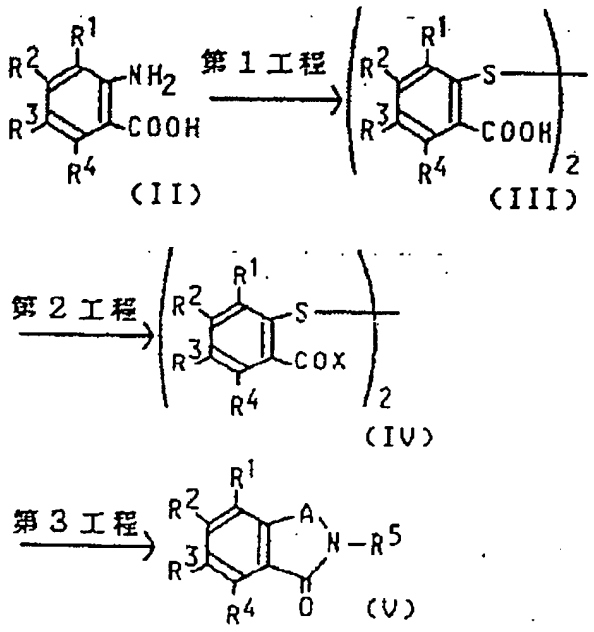
⌈Substituent group B⌋

Lower alkyls, halogen atoms, aminos which may also be substituted by lower alkyls, lower alkoxycarbonyls and aralkyloxycarbonyls.

⌈Substituent group C⌋

Lower alkoxyls, halogen atoms, aryls, and aryls substituted by one or more groups selected from the following [substituent group B].

The compounds contained in the antiulcer agent of this invention are well-known compounds or prepared according to an ordinary method as described below.



→ first process

→ second process

→ third process

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In the above formula, R^1, R^2, R^3, R^4, R^5 and A represent same meanings as above, and X represents a halogen atom such as chlorine, bromine, iodine, etc. or an elimination group of sulfonyloxyl, respectively, e. g., lower alkanesulfonyloxyls such as methanesulfonyloxyl, ethanesulfonyloxyl, etc., lower halogenoalkanesulfonyloxyls such as trifluoromethane-sulfonyloxyl, pentafluoroethanesulfonyloxyl, etc., arylsul-fonyloxyls such as benzenesulfonyloxyl, p-toluenesulfonyloxyl, etc.

The first process is a process wherein the amino group of an anthranil compound (II) is diazotized with a metal nitrite such as sodium nitrite, then reacted with a metal sulfide such as sodium sulfide and converted to a mercapto group to prepare a compound (III).

The reaction is carried out according to a method described in *Organic Synthesis*, Vol. 2, 580, Kats (**6/B**) et al's method (*J. of Organic Chemistry*, **18**, 1380 (1953)) or Davis et al's method (*Advances in Heterocyclic Chemistry*, **14**, 43 (1972)).

The second process is a process wherein the carboxyl group of a compound (III) is converted to an activated carboxyl group (-COX) to prepare a compound (IV), for example, if X is a halogen atom, the halogenation is carried out according to an ordinary method with a thienyl halide such as thienyl chloride, thienyl bromide, thienyl iodide, etc., a sulfuryl halide such as

sulfuryl chloride, sulfuryl bromide, sulfuryl iodide, etc., a phosphorus trihalide such as phosphorus trichloride, phosphorus tribromide, phosphorus triiodide, a phosphorus pentahalide such as phosphorus pentachloride, phosphorus pentabromide, phosphorus pentaiodide or a phosphorus oxyhalide such as phosphorus oxychloride, phosphorus oxybromide, phosphorus oxyiodide, etc.

If X is a sulfonyloxy, the process is carried out according to an ordinary method with a sulfonyl halide such as methanesulfonyl chloride, ethanesulfonyl chloride, methanesulfonyl bromide, ethanesulfonyl bromide, p-toluenesulfonyl chloride, benzenesulfonyl chloride, etc.

The third process is a process wherein a compound (IV) and a compound having a general formula R^5-NH_2 (where R^5 represents same meaning as above) are reacted in the presence of a base in a solvent, and then the sulfur atom is further oxidized according to demand to prepare a compound (V) contained in the antiulcer agent of this invention.

In this process, solvents used are not specially restricted if they do not retard the reaction and dissolve staring materials dissolve to some extent, and aliphatic hydrocarbons such as hexane, heptane, ligroin, petroleum ether, etc.; aromatic hydrocarbons such as benzene, toluene, xylene, etc.; halogenated hydrocarbons such as methylene chloride, chloroform,

carbon tetrachloride, dichloroethane, chlorobenzene, dichlorobenzene, etc.; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane, diethylene glycol dimethyl ether, etc. can be suitably given.

Bases used are not specially restricted if they are used as bases in common reactions, and alkali metal carbonates such as sodium carbonate, potassium carbonate, etc.; alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate, etc.; alkali metal hydrides such as lithium hydride, sodium hydride, potassium hydride, etc.; inorganic bases such as sodium hydroxide, potassium hydroxide, barium hydroxide, etc.; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, etc.; alkali metal mercaptides such as sodium methyl mercaptide, sodium ethyl mercaptide, etc.; organic bases such as triethyl-

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amine, tributylamine, diisopropylethylamine, N-methylmorpholine, pyridine, 4-(N,N-dimethylamino)pyridine, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazacyclo(4,3,0)nona-5-ene, 1,4-diazacyclo[2,2,2]octane (DABCO), 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), etc. or organometallic bases such as butyllithium, lithium diisopropylamide, etc. can be suitably given.

The reaction is carried out at a temperature of 0 - 50°C, preferably 5 - 30°C.

The reaction time mainly depends upon reaction temperature, material compounds or kind of solvents used, but it is commonly 1 hr to 1 day.

Solvents used in the oxidation being a desirable process are not specially restricted if they do not inhibit the reaction and dissolve staring materials to some extent, and aromatic hydrocarbons such as benzene, toluene, xylene, etc.; halogenated hydrocarbons such as methylene chloride, chloroform, etc.; ethers such as ether, tetrahydrofuran, dioxane, dimethoxyethane, etc.; amides such as dimethylformamide, dimethylacetamide, hexamethylphosphoramide, etc.; sulfoxides such as dimethyl sulfoxide, etc.; water; ketones such as acetone, methyl ethyl ketone, etc. or nitriles such as acetonitrile, etc. can be suitably given.

Reagents used are not specially restricted if they are relatively mild oxidants, and they are suitably inorganic oxidants, e. g., manganese oxides such as manganese dioxide, etc.; chromic acids such as chromic acid, etc.; ruthenium oxides such as ruthenium tetroxide, etc.; organic peracids such as m-chloroperbenzoic acid, peracetic acid, etc.; peroxides such as t-butanol peroxide in the presence of a catalyst such as palladium oxide acetylacetonate, etc. or reagents used in a so-called DMSO oxidation (a complex of dimethyl sulfoxide with dicyclohexylcarbodiimde, oxalyl chloride, acetic anhydride or

phosphorus pentachloride or a pyridine-sulfuric anhydride complex), etc.

The reaction is carried out at a temperature of 0 - 100°C, and the reaction time mainly depends upon reaction temperature, material compounds or kind of solvents used, but it is commonly 30 min to 24 hr.

After the reaction is finished, an objective compound of reaction is gathered from the reaction mixture. For example, it is obtained by properly neutralizing the reaction mixture, removing insoluble matter by filtration if it exists, then adding an organic solvent immiscible with water, washing with water and subsequently removing the solvent.

If necessary, the objective compound can be further purified by ordinary methods, e. g., by recrystallization, reprecipitation or chromatography, etc.

[Effects]

Inhibitory Action on H^+,K^+-ATPase *in vitro*

A microzone fraction prepared from a fresh fundi glands of pig in accordance with a Saccomani et al's method [*J. Biol. Chem.*, **251**, 7690 (1976)] was used as a sample of H^+,K^+-ATPase. 0.9 mL of a 40 mM TRIS-acetic acid buffer solution (2 mM magnesium chloride, 20 mM potassium chloride, pH 7.4) containing

20 - 40 :g of the enzyme sample based on protein mass conversion was added into 10 :L of a solution giving by dissolving a compound to be tested in dimethyl sulfoxide, and then reacted at 37°C for 30 min. The enzymic reaction was initiated by adding 0.1 mL of a 20 mM ATP≅2Na solution and then carried out at 30°C for 8 min. The reaction was terminated by adding 1 mL of 10% trichloroacetic acid mixed solution containing 100 mg of active carbon. The reaction solution was centrifuged (3,000 rpm, 15 min), then the concentration of inorganic phosphoric acid in its supernatant was quantified colorimetrically by Fiske-Savarow (Λ(=9≅;9⊥[3) method. The quantity of inorganic phosphoric acid in the reaction solution in the absence of 20 mM potassium chloride was also obtained similarly, and then the H^+,K^+-ATPase activity was obtained by subtracting it from the quantity in the presence of 20 mM potassium chloride. /15

The percentage of inhibition (%) was evaluated from the activity value of a control and an activity value of a compound to be tested at each concentration to obtain the percentage of inhibition on H^+,K^+-ATPase or the 50% inhibition concentration (IC_{50}) was evaluated.

The results are collected in Table 1.

Moreover, in the table,

Ada represents adamantyl,

iBu, isobutyl

tBu, t-butyl

Bz, benzyl,

CPT, cyclopenta[b]thiazolyl

EC, ethoxycarbonyl

ITHI, isothiazolyl

MC, methoxycarbonyl

NA, ∃-naphthyl

Ph, phenyl

iPr, isopropyl

Pyr, pyridyl

THBO, 6-methyl-4,5,6,7-tetrahydrobenzooxazolyl

THBT, 4,5,6,7-tetrahydrobenzothiazolyl

THF, tetrahydrofuryl

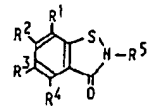
THI, thiazolyl

THID, thiazolidinyl

/15-16

Table 1

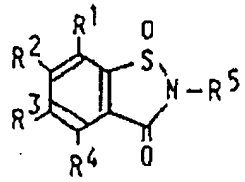
표 1



Comp.	R^1	R^2	R^3	R^4	R^5	H^+,K^+-ATPase Inhibition Activity (:g/mL) or IC_{50}
1	H	H	H	H	-CH_2-MC	IC_{50} = 0.30
2	H	H	H	H	H	IC_{50} = 0.29
3	H	H	CH_2	H	H	37.6% (0.15)
4	H	H	CH_2	H	-CH_2-MC	IC_{50} = 0.13
5	H	Cl	H	H	H	56.6% (0.15)
6	H	H	H	H	-CH_2CH_2-MC	IC_{50} = 0.44
7	H	H	H	H	-CH_2CH=CH_2	47.1% (0.15)
8	H	H	H	H	-CH_2CH_2CN	30.4% (0.15)
9	H	H	H	H	-Bz	IC_{50} = 0.12
10	H	H	H	H	-(R)CH(CH_2)Ph	38.7% (0.15)
11	H	H	H	H	-(S)CH(CH_2)Ph	60.4% (0.15)
12	H	H	H	H	-CH_2(4-OCH_2)Ph	IC_{50} = 0.33
13	H	H	H	H	-(R)CH(S)CH(OH)CH_2)COOBz	IC_{50} = 0.42
14	H	H	H	H	-(4-F)Ph	IC_{50} = 0.25
15	H	H	H	H	-(3,5-diF)Ph	IC_{50} = 0.15
16	H	H	Cl	H	-(4-F)Ph	17.4% (0.15)
17	H	H	H	H	-2-THI	73.0% (0.15)
18	H	H	CH_3	H	-2-THI	61.0% (0.15)
19	H	H	H	H	-iPr	17.8% (0.15)
20	H	H	H	H	-(S)CH(i-Bu)-MC	IC_{50} = 0.29
21	H	H	H	H	-(S)CH($CH_2CH_2SCH_2$)-MC	IC_{50} = 0.22
22	H	H	H	H	-C(=CH_2)-COOBz	IC_{50} = 0.19
23	H	H	H	H	-(S)CH(Bz)-EC	IC_{50} = 0.31
24	H	H	H	H	-(3-CH_2O)Ph	65.2% (0.15)
25	H	H	H	H	-(4-CH_2O)Ph	55.8% (0.15)
26	H	H	CH_3	H	-3-CH_3-2-Pyr	62.5% (0.15)
27	H	H	CH_3	H	-2-oxa-3-THF	IC_{50} = 0.48
28	H	H	CH_3	H	-(3-iPrO)Ph	100% (0.5)
29	H	H	CH_3	H	-4-(CH_2Cl)-2-THI	87.0% (0.5)
30	H	H	CH_3	H	-8-Ada	51.5% (0.5)
31	H	H	CH_3	H	-(2-NH_2)Ph	87.5% (0.5)
32	H	H	H	H	-(3-CH_2O)Ph	65.2% (0.15)
33	H	H	H	H	-(2-CH_2O)Ph	62.7% (0.15)
34	H	H	H	H	-(4-CH_2O)Ph	55.8% (0.15)
35	H	H	H	H	-(4-EC)Ph	33.1% (0.15)
36	H	H	H	H	-(4-$NHCH_2$)Ph	43.0% (0.15)
37	H	H	H	H	-4-Pyr	IC_{50} = 0.15
38	H	H	H	H	-3-Pyr	IC_{50} = 0.15
39	H	H	H	H	-2-Pyr	IC_{50} = 0.15
40	H	H	CH_3	H	-6-OCH_2-3-Pyr	24.7% (0.15)
41	H	H	CH_3	H	-3-CH_2-2-Pyr	62.5% (0.15)
42	H	H	CH_3	H	-2,6-diCH_2O-3-Pyr	45.6% (0.15)
43	H	H	H	H	-2-Cl-4-Pyr	15.4% (0.15)
44	H	H	CH_3	H	-2-THID	IC_{50} = 0.28
45	H	H	CH_3	H	-4-NA-2-THI	28.2% (0.5)
46	H	H	CH_3	H	-2-THBO	IC_{50} = 0.49
47	H	H	CH_3	H	-2-THBT	IC_{50} = 0.50
48	H	H	CH_3	H	-3-Pyr	IC_{50} = 0.17
49	H	OCH_3	OCH_3	H	-4-t-Bu-Ph	IC_{50} = 0.29
50	H	OCH_3	OCH_3	H	-2-MC-Ph	IC_{50} = 0.28
51	H	OCH_3	OCH_3	H	-2,6-di-iPr-Ph	64.8% (0.15)
52	H	OCH_3	OCH_3	H	-2,6-diCH_2-Ph	IC_{50} = 0.30
53	H	OCH_3	OCH_3	H	-3-CH_2-5-ITHI	IC_{50} = 0.15
54	CH_3	H	H	H	-2,6-di-iPr-Ph	23.7% (5)
55	CH_3	H	H	H	-Ph	19.8% (0.5)

Table 1 (Contd.)

Comp.	R^1	R^2	R^3	R^4	R^5	H^+,K^+-ATPase Inhibition Activity (:g/mL) or IC_{50}
	CH_3	H	H	H	-4-Ph—2-THI	40.4% (0.5)
56	CH_3	H	H	H	-4-Pyr	IC_{50} = 0.40
57	CH_3	H	H	H	-2-THBO	IC_{50} = 0.90
58	CH_3	H	H	H	-2-CPT	IC_{50} = 0.80
59	CH_3	H	H	H	-2-THBT	40.9% (0.5)
60	CH_3	H	H	H	-4-NA-2-THI	IC_{50} = 0.70
61	CH_3	H	H	H	-4-(3-OCH_2-Ph)-2-THI	IC_{50} = 0.60
62	CH_3	H	H	H	-3-OBz-2-Pyr	IC_{50} = 6.70
63	CH_3	H	H	H	-2-Cl-4-Pyr	IC_{50} = 0.70
64						
Omeprazole						IC_{50} = 12.0



Comp.	R^1	R^2	R^3	R^4	R^5	H^+,K^+-ATPase Inhibition Activity (:g/mL) or IC_{50}
65	H	H	H	H	-4-F-Ph	IC_{50} = 0.12
66	H	OCH_3	OCH_3	H	-2,6-di-iPr-Ph	27.0% (0.5)
Omeprazole						IC_{50} = 12.0

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As described above, the compounds (I) of this invention have excellent inhibitory action on H^+,K^+-ATPase and are useful for the prevention or treatment of gastrointestinal diseases, etc. of mankind, e. g., gastric ulcer, duodenal ulcer, or Zollinger-Ellison symdrone, etc.

As administration forms of the invented compounds (I), e. g., oral administration with tablet, capsule, granule, powder or syrup, etc. or parenteral administration based on injection or suppository, etc. can be given.

Their dose depends upon symptoms, age, etc. and can be administrated once or several times daily by 0.1 - 100 mg/kg body weight.

Next, the preparation of compounds contained in the antiulcer agent of this invention will be illustrated by giving preparation examples and reference examples, and this invention will be illustrated more specifically by giving preparation examples.

Preparation Example 1

7-Methyl-2-(2',6'-diisopropylphenyl)benzoisothiazolin-3-one

300 mg of an acid chloride synthesized in Reference Example 2 was dissolved in 20 mL of anhydrous methylene chloride, a methylene chloride solution of chlorine gas (1.5 times of mole equiv.) was added under ice cooling and then stirred for about 20 min. After removing the solvent, an anhydrous methylene chloride solution (20 mL) of 0.3 mL of 2,6-diisopropylaniline (2 mole equiv.) and 0.45 mL of triethylamine (4 mole equiv.) was

dropped thereto under ice cooling. After 1 hr stirring, the mixture was washed with water and then dried over magnesium sulfate. The residue was purified by rapid chromatography (silica gel TIC, Rf = 0.2 (developed with methylene chloride) to give 350 mg of the objective compound.

m.p.: 162°C.

NMR spectrum (d-chloroform) * ppm:

1.05 (12H, d, J = 7 Hz); 2.22 (3H, s); 2.63 (2H, qq, J = 7 Hz); 7.0 - 8.0 (6H, m).

Mass spectrum (m/e): 325

IR spectrum (KBr): ν_{max} cm^{-1}:

1675, 1360, 1300.

Preparation Example 2

7-Methyl-2-(4-fluorophenyl)benzoisothiazolin-3-one

2 g of an acid chloride obtained by Reference Example 2 was dissolved in 30 mL of anhydrous methylene chloride, and then 1.8 mL (2.4 mole equiv.) of triethylamine was added. 1.42 g (1.2 mole equiv.) of 4-fluoroaniline was added under ice cooling, and the whole was stirred for 1 hr. After washing with water, the mixture was dried over magnesium sulfate, and the product was purified by chromatography (Rf = 0.5, developed with cyclohexane: ethyl acetate = 2:1) to give 700 mg of the objective compound.

m.p.: 113°C.

NMR spectrum (d-chloroform) * ppm:

6.4 - 8.2 (8H, m).

Mass spectrum (m/e): 245

IR spectrum (Nujol): ν_{max} cm^{-1}:

1650, 1460, 1380, 1320.

Preparation Example 3

7-Methyl-2-(2-chloro-4-pyridyl)benzoisothiazolin-3-one

200 mg of an acid chloride obtained by Reference Example 2 was dissolved in 15 mL of anhydrous methylene chloride. A methylene chloride solution of chlorine gas (1.5 mole equiv.) was added to this solution and then stirred for about 20 min. After removing the solvent, a methylene chloride solution of aforesaid crude sulfenyl chloride was dropped into an anhydrous methylene chloride solution (20 mL) of 152 mg of 2-chloro-4-aminopyridine (2 mole equiv.) and 0.33 mL of triethylamine (4.4 mole equiv.) under ice cooling. After the whole was stirred for 1 hr, the mixture was washed with water and then dried over magnesium sulfate. If the solvent was removed, a crystal precipitated, therefore it was washed with ether to give 120 mg of the objective compound.

NMR spectrum (d-chloroform) * ppm:

2.4 (3H, s); 7.44 (1H, d, J = 5 Hz); 7.5 (1H, s); 7.7 - 8.2 (3H, m); 8.45 (1H, d, J = 5 Hz).

Mass spectrum (m/e): 276

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IR spectrum (KBr): ν_{max} cm^{-1}:

1710, 1578, 1468, 1281, 1081.

Preparation Example 4

2-(4-Fluorophenyl)benzoisothiazolin-1,3-dione

360 mg of 2-(4-fluorophenyl)benzoisothiazolin-3-one synthesized according to Reference Example 1, 2 and Preparation Example 2 (m.p. 113°C) was dissolved in 15 mL of methylene chloride, and then 253 mg (1 equiv.) of m-chloroperbenzoic acid was added under ice cooling, and the whole was stirred at room temperature for 1 hr. After removing the solvent, ethyl acetate was added, washed with a dilute sodium bicarbonate solution followed by water, and then the mixture was dried over magnesium sulfate. After removing the solvent, the product was purified by silica gel TLC (Rf = 0.3, developed with cyclohexane : ethyl acetate = 2:1) to give 300 mg of the objective compound.

m.p.: 129°C.

NMR spectrum (d-chloroform) * ppm:

6.3 - 8.3 (8H, m).

Mass spectrum (m/e): 261

IR spectrum (Nujol): ν_{max} cm^{-1}:

1700, 1460, 1380, 1310, 1225, 1080

Reference Example 1

3,3'-Dimethyl-2,2'-dithiosalicylic acid

5.7 g of sodium sulfide nonahydrate, 730 mg of sulfur (S_2) and 7 mL of water were added in order and dissolved by heating. After cooling, 2.5 mL of an aqueous solution of 870 mg sodium hydroxide was added into a 500 mL three-necked flask under cooling and then stirred as it was. On the other hand, 100 mL of water and 4.5 mL of concentrated hydrochloric acid were added to 3.75 g of 3-methylanthranil and dissolved, 6 mL of an aqueous solution of 1.5 g sodium nitrite was added, then a diazo body made by raising the reaction temperature to room temperature was added to the above solution and stirred for 1 hr. Concentrated hydrochloric acid was added to acidify it, and a crystal was filtered. The resultant crystal was dissolved in a 10% sodium carbonate solution, impurities were removed, then the solution was acidified to give 3 g of the objective compound as crystal.

Reference Example 2

3,3'-Dimethyl-2,2'-dithiosalicylic acid chloride

2.8 g of the carboxylic acid obtained as described above was dissolved in 40 mL of toluene, 5 drops of dimethylformamide

and 1.22 mL (double moles) were further added and then refluxed for 1 hr. If the solvent was removed, a crystal was obtained, then it was washed with n-hexane to give the objective compound quantitatively.

Production Example 1 (hard capsule)

A unit capsule was produced by packing 10 - 100 mg of a powdery active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate in each standard two-piece hard gelatin capsule.

Production Example 2 (tablet)

It was produced by using 10 - 100 mg of a powdery active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of a microcrystalline cellulose, 11 mg of starch and 98.8 mg of lactose.

Production Example 3 (injection)

It was produced by stirring 0.15 - 1.5 wt% of an active ingredient in a 10 vol% of propylene glycol, then making it to a prescribed volume with water for injection and sterilizing it.

Production Example 4 (suspension)

It was so produced as to contain 10 - 100 mg of a pulverized active ingredient, 100 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate and 1.0 g of sorbitol (Japanese Pharmacopoeia) in 5 mL of a solution.